(22) International Filing Date:

(30) Priority data:

WORLD INTELLECTUAL PROPERTY ORGANIZATION International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5: WO 92/06675 (11) International Publication Number: A1 A61K 9/12 (43) International Publication Date: 30 April 1992 (30.04.92) PCT/US91/07574 (21) International Application Number:

US

9 October 1991 (09.10.91)

18 October 1990 (18.10.90) 599,694 (71) Applicant: MINNESOTA MINING AND MANUFAC-TURING COMPANY [US/US]; 3M Center, Post Of-fice Box 33427, Saint Paul, MN 55133-3427 (US).

(72) Inventors: SCHULTZ, Robert, K.; SCHULTZ, David, W. Post Office Box 33427, Saint Paul, MN 55133-3427

(74) Agents: REEDICH, Douglas, E. et al.; Intellectual Property Counsel, Minnesota Mining and Manufacturing Company, Post Office Box 33427, Saint Paul, MN 55133-3427 (US).

(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), GR (European patent), GR (European patent), GR (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European pa-

Published

With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: AEROSOL FORMULATION COMPRISING BECLOMETHASONE 17,21 DIPROPIONATE

(57) Abstract

Pharmaceutical solution aerosol formulations comprising beclomethasone 17,21 dipropionate, ethanol, and a propellant selected from the group consisting of 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane, and a mixture thereof.

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Aerosol formulation comprising beclomethasone 17,21 dipropionate.

5 TECHNICAL FIELD OF THE INVENTION

This invention pertains to solution aerosol formulations suitable for use in administering drugs. In another aspect this invention pertains to formulations comprising becomethasone 17,21 dipropionate.

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BACKGROUND OF THE INVENTION

Pharmaceutical suspension aerosol formulations currently use a mixture of liquid chlorofluorocarbons as the propellant. Fluorotrichloromethane,

dichlorodifluoromethane and dichlorotetrafluoroethane are the most commonly used propellants in aerosol formulations for administration by inhalation.

Chlorofluorocarbons have been implicated in the destruction of the ozone layer and their production is

being phased out. Hydrofluorocarbon 134a (HFC-134a,
1,1,1,2-tetrafluoroethane) and hydrofluorocarbon 227 (HFC227, 1,1,1,2,3,3,3-heptafluoropropane) are viewed as being less destructive to ozone than many chlorofluorocarbon propellants; furthermore, they have low toxicity and vapor pressure suitable for use in aerosols.

Beclomethasone 17,21 dipropionate is commercially available as an aerosol product comprising a suspension of a chlorofluorohydrocarbon solvate of beclomethasone 17,21 dipropionate in

chlorofluorohydrocarbon propellants. Preparation of the solvate requires several processing steps and is required in order to obtain a stable aerosol formulation, i.e., one in which the micronized particles of active ingredient remain in the desired respirable particle size range. A solution formulation of beclomethasone 17,21 dipropionate could simplify formulation manufacture and increase the respirable fraction (i.e., the percentage of active ingredient able to reach the airways of the lung where the pharmaceutical effect is everted)

U.S. Pat. No. 2,868,691 discloses a self-propelling pharmaceutical aerosol formulation comprising i) a medicament; ii) a propellant represented generally by the formula C_H_Cl_F_, wherein m is an integer 5 less than 3, n is an integer or zero, y is an integer or zero, and z is an integer, such that n + y + z = 2m + 2; and iii) a cosolvent which assists in the dissolution of the medicament in the propellant. Ethanol is an example of a cosolvent disclosed in this patent. The above formula 10 representing the propellant component generically embraces HFC-134a. This patent does not, however, disclose beclomethasone 17,21 dipropionate or suggest how stable solution aerosol formulations (i.e., formulations that are chemically stable and exhibit desirable respirable 15 fraction) containing any propellant and beclomethasone 17,21 dipropionate can be prepared.

SUMMARY OF THE INVENTION

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formulation comprising a therapeutically effective amount of beclomethasone 17,21 dipropionate, a propellant comprising a hydrofluorocarbon selected from the group consisting of 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane, and a mixture thereof, and ethanol in an amount effective to solubilize the beclomethasone 17,21 dipropionate in the propellant, the formulation being further characterized in that substantially all of the beclomethasone 17,21 dipropionate is dissolved in the formulation, and the formulation is substantially free of any surfactant.

Certain of the preferred formulations of the invention exhibit very desirable chemical stability and provide respirable fractions significantly greater than commercially available beclomethasone 17,21 dipropionate products. Moreover, the formulations of the invention are convenient to manufacture since no solvate of the active ingredient need be prepared.

The pharmaceutical solution aerosol formulations of the invention are suitable for nulmonant bussel are

DETAILED DESCRIPTION OF THE INVENTION

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All weight percentages recited herein are based on the total weight of the formulation unless otherwise indicated.

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The medicament beclomethasone 17,21 dipropionate is generally present in a formulation of the invention in a therapeutically effective amount, i.e., an amount such that one or more metered volumes of the formulation contains an amount of drug effective to exert the intended therapeutic action. Preferably the medicament will constitute about 0.02 to about 0.6 percent by weight, more preferably about 0.05 to about 0.5 percent by weight of the total weight of the formulation.

Ethanol is generally present in an amount effective to solubilize the beclomethasone 17,21 15 dipropionate in the propellant. Preferably, ethanol constitutes about 1 to about 20 percent by weight of the total weight of the aerosol formulation. More preferably, ethanol constitutes about 2 to about 12 percent by weight 20 and even more preferably about 2 to about 10 percent by weight of the aerosol formulation. Most preferably, ethanol will be present in an amount sufficient to dissolve substantially all of the medicament present in the formulation and to maintain the medicament dissolved over the time period and conditions experienced by commercial 25 aerosol products, but not substantially in excess of said amount. Particularly desirable formulations of the invention, while not containing amounts of ethanol substantially in excess of that required (during 30 manufacture of the formulation) to dissolve the amount of active ingredient employed, may be subjected to a temperature of -20°C. without precipitation of the active ingredient.

The hydrofluorocarbon propellant can be HFC
134a, HFC-227, or a mixture thereof. The propellant
preferably constitutes from about 80 to about 99 percent by
weight, preferably from about 88 to about 98 percent by
weight, and more preferably about 90 to about 98 percent by

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propellant present in the formulations of the invention. However, one or more other propellants (e.g., 1-chloro-1,1-difluoroethane) can also be present.

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The formulations of the invention are substantially free of any surfactant. By "substantially free" as used in the instant specification and claims is meant that the formulations contain no more than 0.0005 percent by weight of a surfactant based on the total weight of the formulation. Preferred formulations contain no surfactant. Presence of a significant amount of a surfactant is believed to be undesirable in the case of solution formulations of beclomethasone 17,21 dipropionate because surfactants such as oleic acid and lecithin seem to promote chemical degradation of the active ingredient when the latter is dissolved in the mixture of HFC-134a and ethanol.

Preferred formulations according to the invention consist essentially of beclomethasone 17,21 dipropionate in an amount of about 0.05 to about 0.35 percent by weight based on the weight of the total formulation, ethanol in an amount of about 2 to about 8 percent by weight based on the total weight of the formulation, and 1,1,1,2-tetrafluoroethane.

The solution formulations of the invention can be prepared by dissolving the desired amount of beclomethasone 17,21 dipropionate in the desired amount of anhydrous ethanol accompanied by stirring or sonication. The aerosol vial may then be filled using conventional cold-fill or pressure-fill methods.

The following examples are provided to illustrate the invention but should not be construed as limiting the invention.

Examples 1 - 7

Formulations containing the following ingredients (TABLE I) in the indicated amounts were prepared with the percentages being expressed in parts by weight based upon the total weight of the particular formulation. The active ingredient complexed in preparing

beclomethasone dipropionate, USP while that employed in preparing the formulations of Examples 1 and 4 was a conventional trichloromonofluoromethane solvate of beclomethasone dipropionate. The formulations of Examples 5 1, 4, 5 and 6 were prepared by i) dissolving the active ingredient in the ethanol; ii) metering the solution obtained above into an aluminum vial and crimping a continuous valve onto the vial; iii) pressure-filling the vial with 1,1,1,2-tetrafluoroethane; iv) chilling the vial to -60°C.; and v) replacing the continuous valve with a 50 10 microliter valve which is available under the trade designation "W303-98" from 3M. The formulations of Examples 2, 3 and 7 were prepared by i) dissolving the active ingredient in the ethanol; ii) metering the solution obtained above into an aluminum vial and crimping a 50 15 microliter pressure-fill valve which is available under the trade designation SpraymiserTM M3652 from 3M onto the vial; and iii) pressure-filling the vial with 1,1,1,2tetrafluoroethane.

The actuator employed in the case of all the formulations was a solution actuator available under the trade designation "M3756" from 3M. The elastomer employed in the valves in the case of all formulations was that available under the trade designation "DB-218" from

American Gasket and Rubber Co. (Chicago, IL.)

TABLE I

<u>Ingredient</u>			<u>E</u>				
	1	2	3	4	5	6	7
Beclomethasone 17,21 Dipropionate	0.1%	0.1%	0.25%	0.3%	0.4%	0.44%	0.5%
Ethanol (anhydrous)	3%	5%	10%	5%	10%	10%	15%
1,1,1,2- Tetra- fluoroethane	96.9%	94.9%	89.75%	94.7%	89.6%	89.56% :	84.5%

The chemical stability of the formulation of Example 4 was determined in respect to recovery of the active ingredient over time when the formulation was stored at 40°C. TABLE II contains the data.

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TABLE II

10	Storage Time (Weeks)	0	2	4	7	12
	% Recovery	101.4, 98.7	101.9, 101.6	100.8, 99.6	99.3, 95.5	100.6 102.6

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The formulation of Example 1 did not exhibit precipitation of the active ingredient on freezing to -60°C.

The respirable fraction provided by the formulations of Examples 1 - 7 was determined using an Anderson MK II Cascade Impactor with the average respirable fraction obtained from each being in excess of 40%. In the case of the formulations of Examples 1 and 4, the respirable fraction was about 76% and about 70%, respectively.

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From the above data, it is believed that the optimum amount of active ingredient for low and high strength products would be about 0.08 and 0.34 percent by

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weight, respectively, based on the total weight of the formulations.

Example 8

5 A mixture containing 1.67 g of beclomethasone 17,21 dipropionate and 160g of cold (-65°C) ethanol was homogenized using a Virtis 45 homogenizer. The resulting suspension was placed in a one gallon stainless steel filling vessel equipped with a stir bar. A 1839 g portion 10 of cold (-65°C) 1,1,1,2-tetrafluoroethane was added to the filling vessel. After about 5 minutes of stirring, a solution was obtained. The resulting formulation contained 0.08 percent by weight of beclomethasone 17,21 dipropionate, 8.0 percent by weight of ethanol and 91.92 15 percent by weight of 1,1,1,2-tetrafluoroethane. formulation was cold filled into aerosol vials and then 50 μ L cold fill valves were crimped onto the vials.

Example 9

Using the general method of Example 8, a formulation containing 0.34 percent by weight of beclomethasone 17,21 dipropionate, 8.0 percent by weight of ethanol and 91.66 percent by weight of 1,1,1,2-tetrafluoroethane was prepared. The formulation was cold filled as a suspension into aerosol vials which were then equipped with 50 μL cold fill valves. The formulation changed from a suspension to a solution as the vials warmed to room temperature.

30 Example 10

A formulation containing 0.3 percent by weight of beclomethasone 17,21 dipropionate, 10 percent by weight of ethanol and 89.7 percent by weight of 1,1,1,2,3,3,3-heptafluoropropane was prepared by i) weighing a 30 mg portion of beclomethasone 17,21 dipropionate into an aerosol vial ii) crimping a continuous valve onto the vial and iii) pressure filling with a solution containing 10

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WHAT IS CLAIMED IS:

- 1. An aerosol formulation comprising a therapeutically effective amount of beclomethasone 17,21 dipropionate, a propellant comprising a hydrofluorocarbon selected from the group consisting of 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane, and a mixture thereof, and ethanol in an amount effective to solubilize the beclomethasone 17,21 dipropionate in the propellant, the formulation being further characterized in that substantially all of the beclomethasone 17,21 dipropionate is dissolved in the formulation, and that the formulation is substantially free of any surfactant.
- 2. A solution aerosol formulation according to Claim 1, comprising between 0.02 and about 0.6 percent by weight beclomethasone 17,21 dipropionate, between about 1 and about 20 percent by weight ethanol, and between about 80 and about 99 percent by weight of said propellant.
 - 3. A solution aerosol formulation according to Claim 1 wherein said beclomethasone 17,21 dipropionate is present in an amount of about 0.05 to about 0.5 percent by weight.
 - 4. A solution aerosol formulation according to Claim 1 wherein said ethanol is present in an amount of about 2 to about 12 percent by weight.
- 5. A solution aerosol formulation according to Claim 1 wherein said ethanol is present in an amount of about 2 to 10 percent by weight.
- 6. A solution aerosol formulation according to
 35 Claim 1 wherein said propellant is present in an amount of
 about 88 to about 98 percent by weight.

- 7. A solution aerosol formulation according to Claim 1 comprising 1,1,1,2-tetrafluoroethane as substantially the only propellant.
- 8. A solution aerosol formulation according to Claim 1 comprising 1,1,1,2,3,3,3-heptafluoropropane as substantially the only propellant.
- 9. A solution aerosol formulation according to
 10 Claim 1 comprising beclomethasone 17,21 dipropionate in an
 amount of about 0.05 to about 0.5 percent by weight,
 ethanol in an amount of about 2 to about 12 percent by
 weight and said propellant in an amount of about 88 to
 about 98 percent by weight.

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- 10. A solution aerosol formulation according to Claim 1 comprising beclomethasone 17, 21 dipropionate in an amount of about 0.05 to about 0.45 percent by weight, ethanol in an amount of about 2 to about 10 percent by weight and said propellant in an amount of about 90 to about 98 percent by weight.
- 11. A solution aerosol formulation according to Claim 1, consisting essentially of beclomethasone 17,21
 25 dipropionate in an amount of about 0.05 to about 0.35 percent by weight, ethanol in an amount of about 2 to about 8 percent by weight, and 1,1,1,2-tetrafluoroethane.
- 12. A solution aerosol formulation according to
 30 Claim 1, wherein the amount of ethanol present is not
 substantially in excess of the amount required to dissolve
 substantially all of the beclomethasone 17,21 dipropionate,
 but is sufficient to permit said formulation to be
 subjected to a temperature of -20°C. without significant
 35 precipitation of said beclomethasone 17, 21 dipropionate.
 - 13. A method of treating bronchial asthma in a

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a formulation according to Claim 1 sufficient to treat the asthmatic condition.

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14. A method of preparing a solution aerosol

5 formulation comprising the step of combining a
therapeutically effective amount of beclomethasone 17,21
dipropionate, a propellant selected from the group
consisting of 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3heptafluoropropane, and a mixture thereof, and an amount of
10 ethanol effective to solubilize the beclomethasone 17,21
dipropionate in the propellant.

INTERNATIONAL SEARCH REPORT

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